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22429	7590	01/10/2007	EXAMINER	
LOWE HAUPTMAN BERNER, LLP			GANGLE, BRIAN J	
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SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE		DELIVERY MODE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,655	DIDEBERG ET AL.	
	Examiner Brian J. Gangle	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 30 October 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 23-48 is/are pending in the application.
 - 4a) Of the above claim(s) 34-47 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 23-33 and 48 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>1/10/2003</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the response filed 10/30/2006 is acknowledged. The traversal is on the following ground(s).

Applicant argues:

1. That all of the identified claim groupings relate technically to the recombinant protein containing concatenated fragments of the PBP2x protein. Applicant states, as an example, that "the antibody arises as a consequence of the protein."

2. That there is no evidence of record that establishes that the claimed aspects of the present invention do not define a contribution over the prior art.

3. That there would be no undue burden to search and examine all of the pending claims.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the identified groups do not all share a common special technical feature, as required by PCT Rules 13.1 and 13.2. For example, the primers of Group IV do not encode the proteins of Group I; these primers would not encode anything that would be bound by the antibodies of Group V; and the nucleic acid molecules of Group III would not necessarily encode proteins to which the antibodies of Group V would bind. Therefore, there is no common special technical feature amongst the identified groups.

Regarding argument 2, as stated above, there is no common feature linking the groups; therefore, there is no feature that defines a contribution over the art, and there is no need to produce prior art as evidence to show that the non-existent feature is not novel.

Regarding argument 3, search and examination burden is not a criterion for determining whether a restriction is proper under PCT Rules 13.1 and 13.2.

The requirement is still deemed proper and is therefore made FINAL.

Claims 23-48 are pending. Claims 34-47 are withdrawn as being drawn to non-elected inventions. Claims 23-33 and 48 are currently under examination.

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth below. Full compliance with the sequence rules is required in response to this office action.

This application fails to comply with the requirements of 37 C.F.R. 1.821-1.825 because it contains amino acid sequences that are not identified. For example, pages 6 and 10 contain sequences that are not identified. Appropriate sequence identifiers should be used to comply with sequence rules. The sequences in the specification should match the sequence listing and computer readable form (CRF) submitted with the application. Applicant is asked to review the specification for sequences that are not identified and correction is required. Applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing", a substitute paper copy of the "Sequence Listing", an amendment of the specification to insert appropriate sequence identifiers, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 3. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

It should be noted that the cited occurrence of improper use is only exemplary and applicant should review the specification to correct any other use of embedded hyperlink and/or other form of browser-executable code.

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Information Disclosure Statement

The information disclosure statement filed 1/10/2005 has been considered. An initialed copy is enclosed.

Claim Objections

Claim 48 is objected to because of the following informalities: Claim 48 is drawn, in part, to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-26, 28-33 and 48 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The amino acid sequence represented by SWISSPROT p14677 and GENBANK 18266817 is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The sequences associated with accession numbers such as SWISSPROT or GENBANK are fluid and can be changed after submission. Therefore, without the sequences of SWISSPROT p14677 or GENBANK 18266817 at the time of invention, one of skill in the art would not be able to identify the amino acid sequences required in the claimed recombinant protein.

Claims 23-26, 28-33 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

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Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The instant claims are drawn to a recombinant protein obtained from *Streptococcus pneumoniae* PBP2x protein which comprises concatenated fragments corresponding, respectively, to amino acids located between positions 74 to 90, 186 to 199, 218 to 228 and 257 to 750, with reference to the sequence of the PBP2x protein of the strain R6 (SWISSPROT p 14677 or GENBANK 18266817), each one of said fragments being preceded by a peptide fragment of 1 to 7 amino acids. The claims further include said recombinant protein where said *Streptococcus pneumoniae* PBP2x protein has a sequence identity which is at least 30% or 50% identical with the sequence of SWISSPROT p 14677, and a fragment of at least 7 amino acids of the claimed recombinant protein.

The specification does not describe the sequence of the PBP2x protein. The claims require specific residues in said sequence, but there is no information regarding the sequences associated with accession numbers SWISSPROT p 14677 or GENBANK 18266817. In addition, the aforementioned claims encompass recombinant proteins which require specific residues from a protein which has only 30% homology to the PBP2x protein. The claims also encompass fragments of the PBP2x protein that are only 7 amino acids in length.

The sequences associated with accession numbers such as SWISSPROT or GENBANK are fluid and can be changed after submission. Therefore, without a baseline sequence, one cannot envision the claimed proteins. Further, these claims encompass a vast genus of polypeptides that have no correlation between their structure and function. The specification provides insufficient written description to support the genus encompassed by the claim. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that

"applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the

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complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid and/or protein itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2datl966.

Therefore, only SEQ ID NO:1, but not the full breadth of the claims, meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

Claims 23-26, 28-33 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant protein which has the sequence of SEQ ID NO:1, does not reasonably provide enablement for the claims as drawn. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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The instant claims encompass recombinant proteins obtained from *Streptococcus pneumoniae* PBP2x protein which comprises concatenated fragments corresponding, respectively, to amino acids located between positions 74 to 90, 186 to 199, 218 to 228 and 257 to 750, with reference to the sequence of the PBP2x protein of the strain R6 (SWISSPROT p 14677 or GENBANK 18266817), each one of said fragments being preceded by a peptide fragment of 1 to 7 amino acids. The claims further include said recombinant protein where said *Streptococcus pneumoniae* PBP2x protein has a sequence identity which is at least 30% or 50% identical with the sequence of SWISSPROT p 14677, and a fragment of at least 7 amino acids of the claimed recombinant protein. The sequences associated with accession numbers such as SWISSPROT or GENBANK are fluid and can be changed after submission. Therefore, without a baseline sequence, one cannot make or use the claimed proteins. Further, these claims encompass a vast genus of polypeptides that have no correlation between their structure and a specific function. The specification does not describe the sequence of the PBP2x protein. The specification does disclose SEQ ID NO:1, which ostensibly meets the limitations of the claims. However, the claims require specific residues in said sequence, but there is no information regarding the sequence SWISSPROT p14677 or GENBANK 18266817. The specification further does not disclose which fragments of the PBP2x protein are necessary to achieve a specific function. Protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions

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(column 2, page 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess *et al.* (J. of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar *et al.* (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, fragments of PBP2x that maintain the function of PBP2x could not be predicted. Additionally, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, column 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, column 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, column 3). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, column 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399, paragraph bridging columns 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, paragraph bridging cols 1 and 2). Clearly, given not only the teachings of Bowie *et al.*, Lazar *et al.* and Burgess *et al.* but also the limitations and pitfalls of using computational sequence

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analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the claimed proteins could not be predicted based on sequence identity to PBP2x. Clearly, it could not be predicted that polypeptide or a variant that shares only partial homology with a disclosed protein will function in a given manner (i.e. PBP2x carboxypeptidase activity). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use the claimed genus of proteins. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-33, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is rendered vague and indefinite by the phrase "a recombinant protein obtained from *Streptococcus pneumoniae* PBP2x protein, which recombinant protein comprises concatenated fragments corresponding, respectively, to amino acids located between positions 74 to 90, 186 to 199, 218 to 228, and 257 to 750." It is not clear how one obtains a recombinant protein from a protein. It is further not clear what is meant by the term "corresponding." Does this mean that the concatenated fragments must have 100% sequence identity with amino acids 74 to 90, 186 to 199, 218 to 228, and 257 to 750; or does this merely mean that some of the amino acids that are found between positions 74 to 90, 186 to 199, 218 to 228, and 257 to 750 must also be found in the recombinant protein? Finally, applicants have used the phrase "between positions 74 to 90, 186 to 199, 218 to 228, and 257 to 750." Is this meant to be inclusive, or is applicant referring to amino acids 75-89, 187-198, 219-227, and 258-749?

Claim 23 is rendered vague and indefinite by the use of the terms SWISSPROT p14677 and GENBANK 18266817. These terms refer to accession numbers for amino acid sequences.

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However, the sequences associated with a given accession number can be modified, thereby rendering the scope and limitations of the claims uncertain.

Claim 24 is rendered vague and indefinite by the phrase "wherein the peptide fragment comprises amino acids of said *Streptococcus pneumoniae* PBP2x protein located between positions -1 to -7, relative to the residues at positions 74, 186, 218 and 257, or between positions +1 to +7, relative to the residues at positions 90, 199 and 228, as defined in claim 23, or both." First, according to the parent claim, the concatenated fragments can only be separated by a maximum of 7 amino acids. However, claim 24 encompasses the protein where there are amino acids in positions -7 to -1 and +1 to +7 of each fragment, which would create a chain of 14 amino acids that separates the concatenated fragments. Further, it is not clear what these fragments are meant to contain. Are the fragments meant to contain any amino acid that can be found in said positions on the normal PBP2x protein, are they meant to have 100% sequence identity with the amino acids in those positions on the normal PBP2x protein, or are these positions on the recombinant protein meant to contain any amino acid found in the normal PBP2x protein?

Claim 25 is rendered vague and indefinite by the phrase "amino acids comprising alanine, serine, glycine and threonine or a combination thereof." First, it is not clear how an amino acid can comprise an amino acid, or how an amino acid can comprise a combination of amino acids. Second, according to the claim, the fragment must contain at least alanine, serine, glycine and threonine. If it has these, it already has a combination thereof, so it is not clear what limitations are engendered by the addition of the phrase "a combination thereof." Third, it is not clear, based on the lack of a final serial comma, whether the "combination thereof" is meant to be a combination of glycine and threonine only, or of any of the listed amino acids.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,

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except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 33 is rejected under 35 U.S.C. 102(e) as being anticipated by Doucette-Stamm *et al.* (US Patent 6,699,703, filed 5/2000).

The instant claim is drawn to a peptide which comprises a fragment of at least 7 amino acids of the mini-PBP2x protein of claim 23, which peptide includes at least one residue comprising those located at positions 74, 90, 186, 199, 218, 228 and 257 of the PBP2x protein of the strain R6.

Doucette-Stamm *et al.* disclose a peptide (SEQ ID NO:4010) which comprises a fragment of 20 amino acids that match amino acids 4-24 of the mini-PBP2x protein. The first amino acid of this fragment is the same as the one located at residue 74 of the PBP2x protein of the strain R6 (see attached search results from SCORE).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brian Gangle
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